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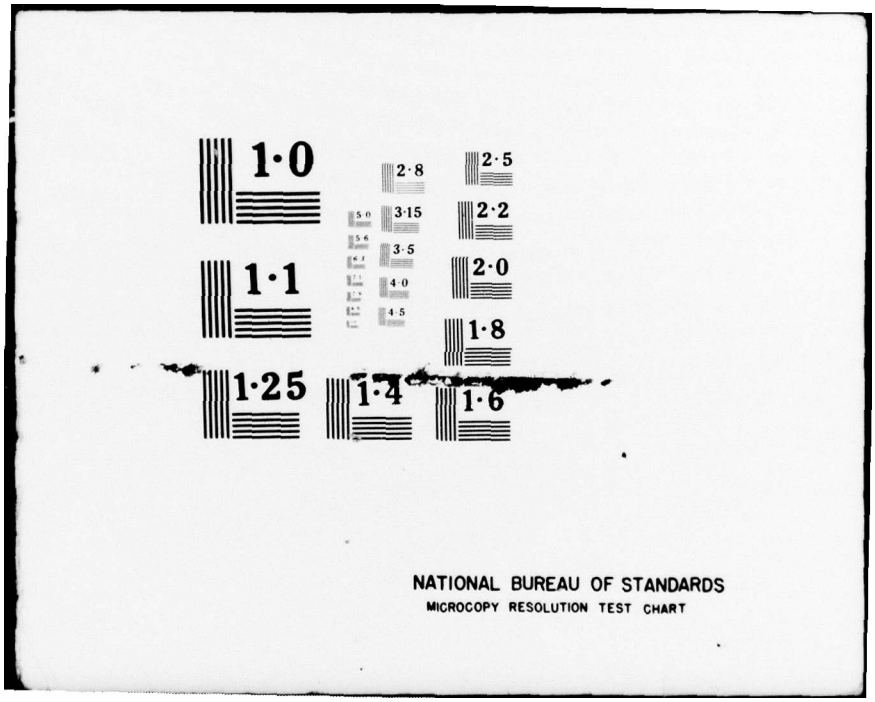
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(6) THE EFFECTS OF ACUTE ALTERATIONS IN HEMODYNAMICS, OXYGEN AVAILABILITY AND ACID-BASE BALANCE ON THE PERMEABILITY OF THE GASTRIC MUCOSA.

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Using a previously described model for acute gastric mucosal ulcerogenesis (Gastroent. 68: 699, 1975), studies ~~carried out in this laboratory during the period covered by the progress report~~ indicated that the glycine conjugates of cholic acid possesses a potential for ulcerogenesis equal to that of the taurine conjugates; that acute ulcerogenesis is associated with a significant reduction in gastric mucosal ATP content; and that the severity of mucosal injury under these circumstances is bile acid concentration dependent.

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I. TITLE OF RESEARCH:

THE EFFECTS OF ACUTE ALTERATIONS IN HEMODYNAMICS, OXYGEN AVAILABILITY, AND ACID-BASE BALANCE ON THE PERMEABILITY OF THE GASTRIC MUCOSA

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III. PERIOD COVERED:

1 October 1975 through 30 September 1976

IV. PROGRESS REPORT

(1) Ulcerogenic Potential of Glycine vs Taurine Conjugates of Cholic Acid

Since the ratio of glycine:taurine conjugates of the primary bile acids in human hepatic bile is approximately 4 to 1, studies have been undertaken to assess the ulcerogenic potential of each of these conjugates of cholic acid in vascularized chambered wedges of proximal canine gastric wall. Preliminary studies indicated that, at pH 1, the maximal concentration of glycocholate which can be solubilized in a liter of solvent (ATS=100mM HCl, 60mM NaCl) is 1mM, in accordance with the pKa and precipitation characteristics of glycocholic acid. Accordingly, the ulcerogenic potential of this concentration of both glycocholic and taurocholic acid was evaluated in animals subjected to three sequential study periods: (1) ATS, (2) ATS+1mM bile acid, (3) ATS+1mM bile acid + vasopressin, VP, 0.01U/Kg.min. delivered intraarterially. A splenectomy in-situ was performed concomitantly. The results (± SEM):

	ATS	ATS+GC	ATS+TC	ATS+VP	ATS+VP+GC	ATS+VP+TC
▲H+(μEq)	-50±24	-121±47	-127±15	-84±34	-279±50	-243±53
▲Na+(μEq)	+78±29	+202±41	+146±37	+57±8	+219±56	+304±47
$\overline{PD}$(mV)	-65±1	-59±3	-58±2	-28±2	-30±5	-27±3
AC(ml/min)	2.83±0.27	5.41±1.32	4.79±0.51	1.57±0.23	1.87±0.39	1.13±0.27
Lesion Index	0	0	0	0.2±0.3	2.5±0.3	2.9±0.4

These data indicate that (1) glycine conjugates of cholic acid cause an increase in gastric mucosal nutrient blood flow comparable to that observed with taurine conjugates in the same concentration and, (2) that, in the presence of ischemia, glycine conjugates of cholic acid possess a potential for ulcerogenesis equal to taurine conjugates.

(2) The Role of ATP in Gastric Mucosal Ulcerogenesis

Recent studies indicate that, in the rat, hemorrhagic shock is associated with a significant reduction in mucosal ATP content. ATP levels are further reduced by concomitant topical application of 30mM sodium taurocholate. The present study was designed to correlate mucosal ATP levels with ulcerogenesis in the model described above. Four groups of animals were studied during 2 consecutive 30 minute study periods. Group one was subjected during both periods to topically applied acid test solution (ATS) during concomitant splenic artery infusion with 0.9% NaCl. Group two: (1) ATS, (2) ATS containing 5mM taurocholic acid (TC), again during splenic artery infusion with saline. Group three: (1) ATS, (2) ATS+ vasopressin delivered at a rate of 0.1U/Kg.min intraarterially via the splenic artery. Group four: (1) ATS, (2) ATS+vasopressin+5mM TC. At the conclusion of the second study period, in every animal, the mucosa and submucosa were rapidly stripped from the muscular layers and quick frozen in liquid nitrogen. Subsequently, the mucosa was powdered and ATP content/gm wet weight was determined using the fire fly assay technique. Protein content/gm wet weight was assessed using the method of Lowry. Additional parameters evaluated during the final study period in each animal included the net fluxes of H+ and Na+, the PD, the AC, and the degree of mucosal damage induced (the lesion index = LI) graded 0-4 by an independent observer unaware of the experimental protocol. The results of the study are summarized below:

	ATS	ATS+TC	ATS+VP	ATS+TC+VP
Δ H+(μEq)	-70±36	-417±126	-85±35	-530±57
Δ Na+(μEq)	+135±16	+310±85	+75±20	+186±31
$\overline{PD}$(mV)	-64±3	-29±3	-28±2	-27±1
AC(ml/min)	1.66±0.14	2.82±0.36	1.02±0.14	0.96±0.21
LI	0	0	0.2±0.1	3.8±0.2
ATP(μM/mgm protein)	5.36±0.52	5.41±0.44	4.36±0.38	3.38±0.42*

*Significant difference vs. ATS, ATS+TC, ATS+VP

These data suggest that, compared to the circumstance observed with ATS alone, neither topical bile acid application nor mucosal ischemia, in and of themselves, result in significant depletion of mucosal ATP content. On the other hand, the acute ulcerogenesis

observed using the combination of topical bile acid at low pH and mucosal ischemia is associated with a significant reduction in mucosal ATP content. The present study does not permit a statement as to whether this reduction is the cause of or the result of the ulcerogenic process.

(3) Bile Acid Dose Dependence of Acute Gastric Mucosal Ulcerogenesis

Experimentally derived data which tend to support the hypothesis outlined above suffer from a common problem: the concentrations of bile acids used to induce acute gastric mucosal damage are in all probability pharmacologic rather than physiologic. Bile acid reflux was assessed in 11 post-operative patients, 9 of whom refluxed bile acid/salt in a mean intragastric concentration of 1.87±0.24mM (range=0.34 to 4.88). Accordingly, a study was designed to assess the ulcerogenic potential of physiologic bile acid concentrations. Using vascularized chambered canine gastric mucosa, groups of animals (n=5 each group) were studied during 3 consecutive periods. Group A= topical acid test alone (ATS) during periods (1), (2), and (3); Group B (1) ATS, (2) ATS, (3) ATS+vasopressin (VP=0.1U/Kg.min via the splenic artery); Group C= (1) ATS, (2) ATS+topical 1mM taurocholic acid (TC), (3) ATS+1TC+VP; Group D= (1) ATS, (2) ATS+2TC, (3) ATS+2TC+VP; Group E= (1) ATS, (2) ATS+5TC, (3) ATS+5TC+VP. Parameters evaluated included the net fluxes of H^+ and Na^+, the PD, the AC, and lesion formation, graded by an independent observer using photographs.

The results indicated that, in non-ischemic mucosa, topical bile acid at low pH produced no ulcers, a significant concentration dependent increase in H^+ "back diffusion" and fall in PD, and a nonconcentration dependent increase in MBF. The data also demonstrated that, (1) as expected, the combination of topical acid, topical bile acids, and mucosal ischemia was acutely ulcerogenic; and that (2) the severity of mucosal injury was bile acid concentration dependent; and that (3) acute mucosal damage occured in the presence of physiologic bile acid concentrations, i.e. those routinely found in the gastric lumen of post-operative patients.

(4) Effect of Topical Prostaglandin E_2 on Acute Gastric Mucosal Ulcerogenesis

As indicated in an earlier progress report, the research effort in the laboratory has been substantially hampered during the current year by the scarcity of vasopressin. This scarcity has been occasioned by the fact that slaughter facilities have been forced to alter their method of sacrificing animals, such that the pituitary gland is currently being destroyed. We have been fortunate in obtaining a small volume of vasopressin and accordingly have had to revise the research plan in such a way as to maximize its use. Thus, in this particular study, only control data has been obtained using a small does of intraarterial vasopressin, 0.01U/Kg.min. Control animals have been subjected either to (1) ATS, (2) ATS, (3) ATS+TC, or (1) ATS, (2) ATS+VP, and (3) ATS+VP+TC. The data indicate that the combination of topical acid, topical bile acid, and vasopressin in the dose

employed is acutely and severely ulcerogenic as expected, although the magnitude of lesion formation is considerably less than that observed previously using vasopressin, 0.1U/Kg.min.

(5) Patient Studies

Because of the turnover of professional personnel at the burn unit at the Brook Army Hospital, the proposed patient study was only recently initiated. Approximately 8 severely burned patients have been studied in a pilot fashion. Total bile acid content and concentration is being analyzed in the obtained samples.

V. PUBLICATIONS

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Ritchie, W. P., Jr.: Bile Acids, the "Barrier", and Reflux Related Disorders of the Gastric Mucosa. Manuscript submitted to Surgery.

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